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Bone Marrow Examination in Cases of New-onset Pancytopenia: A Four-year Study from a Medical College in the Rural Hilly Setting of Western Himalayas, India

Rashmi Kaul Raina[1], Sujeet Raina[2]*
[1]Department of Pathology, Dr. Rajendra Prasad Government Medical College (RPGMC), Tanda, Kangra 176001 (HP), India.
[2]Department of Medicine, Dr. Rajendra Prasad Government Medical College (RPGMC), Tanda, Kangra 176001 (HP), India.

***Correspondence:** sujeetrashmishera@yahoo.co.in

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Abstract
New-onset pancytopenia is a common diagnostic challenge. Pancytopenia is an indication for bone marrow examination. The present study has been carried out to determine the frequencies of various etiologies of pancytopenia based on bone marrow morphology in a defined geographical location. All cases of new-onset pancytopenia, diagnosed on peripheral smear and seen over a four-year period from January 2012 to December 2015 in the department of pathology, were analysed. Patients lacking representative bone marrow in the aspirate or receiving chemotherapy were excluded. Out of 69 cases, 29 were males and 40 were females. Most of the patients were in the age group of 19-60 years (52.2%). Nineteen (26.1%) of them were less than 18 years old. The three major causes of pancytopenia were: megaloblastic anemia (hypercellular marrow with megaloblastic erythropoiesis) in 25 (36.2%) cases, hypercellular marrow with dimorphic erythropoiesis in 13 (18.8%) cases, and haematological malignancies in 12 (17.4%) cases of the study. Bone marrow examination along with laboratory evaluation helps to establish specific diagnosis in cases of new-onset pancytopenia.

Keywords: Pancytopenia; Megaloblastic anemia; Aplastic anemia; Etiology.

1. INTRODUCTION

Pancytopenia is defined as the reduction of all the three formed elements (platelets, red blood cells, and white blood cells) of blood below the normal reference [1]. Pancytopenia is a serious hematological problem, and bone marrow study doesn't always accurately diagnose the etiology of pancytopenia. The spectrum of etiologies ranges from benign conditions, such as infection, nutritional deficiency, and drug effect, to hematologic malignancies, such as lymphoma and acute leukemia [2]. Review of published literature reveals geographic variation in the distribution of causes leading to pancytopenia [2-12]. We present our experience in bone marrow examination in the evaluation of 69 cases of pancytopenia from a tertiary-care centre located in Shivalik and the Lesser Himalayan region of Himachal Pradesh. The patients belonged to the geographical location situated at an altitude from 350 m to 3,000 m above mean sea level. This gives us an insight into the epidemiological data on the etiological profile of pancytopenia from the population of this region.

2. MATERIALS AND METHODS

This cross-sectional record-based observational study was conducted in a medical college in the rural hilly setting of Himachal Pradesh, located in the Northern India. The hospital caters to the rural hilly population of the physiogeographic zone of Shivalik and Lesser Himalayas of the state of Himachal Pradesh, India. Data was collected from our pathology department's records from January 2012 to December 2015 which include bone marrow aspiration and/or biopsies accompanied by a requisition form reporting pancytopenia as an indication or a concurrent complete blood count (CBC) and/or peripheral blood smear evaluation reporting pancytopenia. Recorded information was entered in a precoded proforma which included details on haematological parameters and diagnosis. Current cut-offs were used to make the diagnosis of pancytopenia. Hematologic malignancies were classified according to the 2008 World Health Organization criteria. Children were defined as patients 18 years or younger. Patients lacking representative bone marrow in the aspirate, having a history of hematolymphoid neoplasia or receiving chemotherapy were excluded. The study was approved by the Institutional Ethics Committee. The data, thus collected, was analyzed on a Microsoft Excel 2010 sheet, and percentages were calculated.

3. RESULTS

Bone marrow examinations of 69 patients, fulfilling the criteria of inclusion, were analyzed. Twenty nine cases were males and 40 were females with female to male ratio of 1.3:1. Eighteen cases were children (<18 years). Age distribution is shown in Table 1.

Table 1: Showing age distribution.

Age group (years)	Number (%)			Mean age ± SD		
	Male	Female	Total	Male	Female	Total
⩽**18**	9 (13.0)	9 (13.0)	18 (26.1)	13.67 ± 4.97	11.78 ± 3.86	12.72 ± 4.43
19-60	15 (21.7)	21 (30.4)	36 (52.2)	40.87 ± 14.40	37.76 ± 13.40	39.06 ± 13.71
⩾**61**	5 (7.2)	10 (14.5)	15 (21.7)	69.20 ± 5.21	71.20 ± 9.86	70.53 ± 8.44
Total	29 (42.0)	40 (58.0)	69 (100.0)	37.31 ± 21.97	40.27 ± 23.53	39.03 ± 22.77

p values were not significant.

Table 2: Bone marrow diagnosis with new onset pancytopenia.

Diagnosis	⩽18 years n = 18 (%)			19-60 years n = 36 (%)			⩾61 years n = 15 (%)			Total n = 69 (%)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Hypercellular marrow with megaloblastic erythropoiesis	4 (22.2)	3 (16.6)	7 (38.8)	6 (16.6)	8 (22.2)	14 (38.8)	1 (6.6)	3 (20)	4 (26.6)	11 (15.9)	14 (20.3)	25 (36.2)
Hypercellular marrow with dimorphic erythropoiesis	2 (11.1)	1 (5.5)	3 (16.6)	2 (5.5)	5 (13.8)	7 (19.4)	1 (6.6)	2 (13.3)	3 (20)	5 (7.2)	8 (11.6)	13 (18.8)
Hematological malignancies	2 (11.1)	2 (11.1)	4 (22.2)	2 (5.5)	4 (11.1)	6 (16.6)	1 (6.6)	1 (6.6)	2 (13.3)	5 (7.2)	7 (10.1)	12 (17.4)
Hypercellular marrow with normoblastic erythropoiesis	–	1 (5.5)	1 (5.5)	2 (5.5)	1 (2.7)	3 (8.3)	1 (6.6)	1 (6.6)	2 (13.3)	3 (4.3)	3 (4.3)	6 (8.7)
Aplastic anemia/ hypocellular marrow	1 (5.5)	2 (11.1)	3 (16.6)	–	1 (2.7)	1 (2.7)	–	1 (6.6)	1 (6.6)	1 (1.4)	4 (5.8)	5 (7.2)
Hypercellular marrow with micronormoblastic erythropoiesis	–	–	–	1 (2.7)	2 (5.5)	3 (8.3)	–	–	–	1 (1.4)	2 (2.9)	3 (4.3)
Hypercellular marrow with macronormoblastic erythropoiesis	–	–	–	–	–	–	–	1 (6.6)	1 (6.6)	–	1 (1.4)	1 (1.4)
Metastatic adenocarcinoma	–	–	–	–	–	–	1 (6.6)	–	1 (6.6)	1 (1.4)	–	1 (1.4)
Leishmaniasis	–	–	–	1 (2.7)	–	1 (2.7)	–	–	–	1 (1.4)	–	1 (1.4)
Normal bone marrow	–	–	–	1 (2.7)	–	1 (2.7)	–	1 (6.6)	1 (6.6)	1 (1.4)	1 (1.4)	2 (2.9)

Results of the morphological diagnosis of new-onset pancytopenia are shown in Table 2. Common diagnoses were hypercellular marrow with megaloblastic erythropoiesis in 25 (36.2%), hypercellular marrow with dimorphic erythropoiesis in 13 (18.8%), hematological malignancies in 12 (17.4%), hypercellular marrow with normoblastic erythropoiesis in 6 (8.7%), and aplastic anemia in 5 (7.2%) cases. In one patient, visceral leishmaniasis was confirmed by the detection of Leishman-Donovan (LD) bodies (Figure 1). In one case, metastatic adenocarcinoma was observed. Among patients with hematological malignancies, six patients had acute leukemia, three had myelodysplastic syndrome (refractory cytopenia with multilineage dysplasia), two had plasma cell neoplasm, and one had chronic lymphocytic leukemia.

4. DISCUSSION

A wide variety of disorders can cause pancytopenia. The frequency of various etiologies differs considerably with the difference in geography, ethnicity, age, and socioeconomic status among different populations. In resource-poor settings, megaloblastic anemia and aplastic anemia are frequently cited as leading causes of pancytopenia, while hematologic malignancies are generally frequently reported as leading causes of pancytopenia in industrialized nations. The difference is compounded by the lack of

Figure 1: Photomicrograph showing megakaryocyte with engulfed Leishman Donovan (LD) bodies. (Giemsa, X 1000).

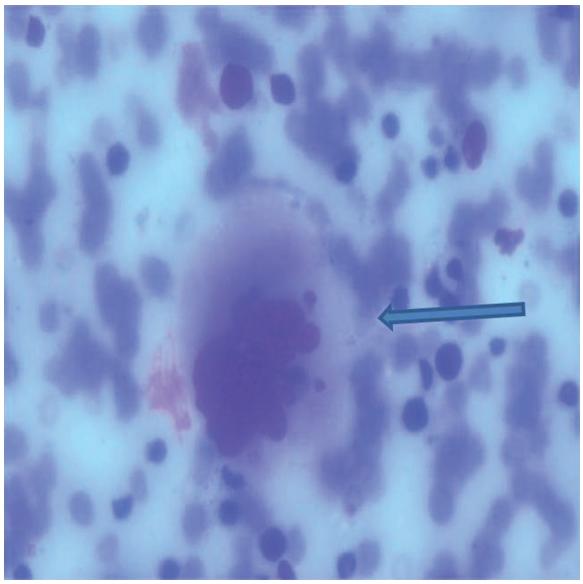

Table 3: Frequency of various causes of pancytopenia in different studies.

Study	Country	Year	No. of cases	Most common cause (%)	Second most common cause (%)	Third most common cause (%)
Kumar *et al.* [3]	India	2001	166	Aplastic anemia (29.51)	Megaloblastic (22.28)	Acute leukemia (18.07)
Khunger *et al.* [4]	India	2002	200	Megaloblastic anemia (72)	Aplastic anemia (14)	Others (24.3)
Niazi *et al.* [5]	Pakistan	2004	89	Aplastic anemia (38.27)	Megaloblastic anemia (24.7)	Hypersplenism (18.75)
Jha *et al.* [6]	Nepal	2008	148	Hypoplastic marrow (29)	Megaloblastic anemia (23)	Hematological malignancy (21)
Santra *et al.* [7]	India	2010	111	Aplastic anemia (22.72)	Hypersplenism (11.7)	Kala azar (9)
Gayathri *et al.* [8]	India	2011	104	Megaloblastic anemia (74)	Aplastic anemia (18)	Subleukemic leukemia (3.85)
Naseem *et al.* [9]	India	2011	571	Aplastic anemia (43)	Megaloblastic anemia (13.7)	
Weinzierl *et al.* [10]	USA	2013	250	MDS (44)	AML (31)	Aplastic anemia (22)
Devitt *et al.* [2]	USA	2014	132	AML (26)	MDS (17)	Unremarkable (14)
Desalphine *et al.* [11]	India	2014	50	Aplastic anemia (26%)	Normoblastic erythroid hyperplasia (22%)	Megaloblastic (16%)
Govindaraj *et al.* [12]	India	2015	50	Megaloblastic anemia (44)	Combined nutritional anemia (20%)	Hypersplenism (12)

AML: Acute myeloid leukemia; MDS: Myelodysplastic syndrome.

a universal definition for pancytopenia to be followed globally [13]. Table 3 shows the various causes of pancytopenia in different studies conducted in different countries [2-12].

The commonest cause of pancytopenia in the present study was megaloblastic anemia (36.2%). The prevalence of megaloblastic anemia in other studies varied from 0.8% to 72% [3-12, 14]. This wide variation of the prevalence of megaloblastic anemia depends on the status of nutritional anemia in that particular region of study. Higher prevalence of megaloblastic anemia reflects nutritional deficiency/anemia in our region also. Folate and vitamin B12 deficiencies are classic causes of megaloblastic anemia, and although these deficiencies commonly present with anemia and thrombocytopenia, they can occasionally present with pancytopenia. In India, nutritional deficiencies of vitamin B12 and/or folate are very common and often lead to pancytopenia. Regardless of the etiology, bone marrow aspiration and biopsy are quite characteristic and demonstrate a hypercellular marrow with erythroid hyperplasia and megaloblastic maturation. The second commonest cause of pancytopenia in our study was hypercellular marrow with dimorphic erythropoiesis reflecting the onset of iron-deficient erythropoiesis in

megaloblastic anemia. This again highlights the prevalence of nutritional anemia in our population. In our study of new-onset pancytopenia, hematological malignancies were the third most frequent cause (17.4%). Six patients had acute leukemia. Three had myelodysplastic syndrome and all had refractory cytopenia with multilineage dysplasia. Of the remaining causes, plasma cell neoplasm accounted for two cases and chronic lymphocytic leukemia for one. Hematopoietic neoplasms, like acute lymphoblastic leukemias in children, acute myeloid leukemias in adults, the spectrum of myelodysplastic syndromes in adults and occasionally myeloproliferative diseases, can present with pancytopenia. Non-Hodgkin lymphomas and Hodgkin's lymphoma can also lead to pancytopenia, but such presentations are rare unless there is significant bone marrow replacement, fibrosis, autoimmune cytopenias, or splenomegaly. Plasma cell myeloma can rarely present with pancytopenia. The fourth commonest cause of pancytopenia in this study was normoblastic erythroid hyperplasia, seen in six cases (8.7%). The relationship between normoblastic erythroid hyperplasia and anemia is uncertain. It is possible that some of these cases represent one phase in the evolution of hypoplasia/aplasia, while some may be cases of refractory anemia. Criteria for differentiation of these groups remain unsatisfactory, and these patients should be kept under regular hematological follow-up [2]. Aplastic anemia was seen in 5 (7.2%) cases. Both bone marrow aspirations and biopsy were performed, and marrow smears with markedly decreased cellularity and increased fat to cell ratio were diagnosed as hypoplastic marrow, and the possibility of aplastic anemia was suggested based on pancytopenia and bone marrow hypocellularity. The incidence of aplastic anemia quoted from the West is 10-25% [2]. In studies conducted in various places of the subcontinent, the prevalence of aplastic anemia is between 7.7% and 43% [3-9, 11]. In the present study, the prevalence is 7.2%. The prevalence of aplastic anemia is higher in pediatric patients as well as in studies by advanced research institutes in India where it may be overrepresented because of the referrals from resource-limited settings [9]. One of the patients had metastatic adenocarcinoma as the etiology of new-onset pancytopenia. Marrow space–infiltrating lesions lead to pancytopenia through direct replacement, interference with ongoing hematopoiesis, or concomitant fibrosis. Metastatic carcinoma can also lead to bone marrow involvement and subsequent marrow fibrosis, but this has been observed in fewer than 10% of patients and is most common in patients with lung, breast, or prostate carcinoma. Visceral leishmaniasis was diagnosed in one patient. Amastigotes of *Leishmania donovani* were seen both intracellularly and extracellularly. The finding is significant because the patient was a native of the nonendemic region of visceral leishmaniasis and had never visited the endemic region in his life. Clinical picture, biochemistry, and bone marrow findings were consistent with acquired hemophagocytic lymphohistiocytosis (HLH) associated with pancytopenia in this patient. Visceral leishmaniasis has been frequently reported as an etiology of pancytopenia in India [3, 7]. Normal bone marrow accounted for two cases (2.9%). Normal bone marrow in pancytopenic patients can result due to sequestration and/or destruction of cells by the action of antibodies or trapping of normal cells in a hypertrophied and overreactive reticuloendothelial system.

Bone marrow aspiration and biopsy evaluation is of utmost importance to evaluate the causes of new-onset pancytopenia and plan further investigations. Aspiration and biopsy complement each other; aspiration smears are superior for morphological details, while biopsy provides a more reliable index of cellularity and often reveals bone marrow infiltration, fibrosis, and granulomas. The varied causes of pancytopenia depend on demographic factors.

Author Contributions

Conceived and designed the study: SR, RKR; Collected the data: RKR; Analyzed the data: RKR, SR; Prepared the manuscript: SR, RKR.

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Conflict of Interest

None.

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